

Hypertension drug trials based on ambulatory blood pressure monitoring: when is a double-blind controlled design needed?

Gianfranco Parati^{a,b} and Jan A. Staessen^c

Journal of Hypertension 2003, 21:1237–1239

^aDepartment of Clinical Medicine, Prevention and Applied Biotechnologies, Milano-Bicocca University and ^bCardiology II, S. Luca Hospital, Istituto Auxologico Italiano, Milano, Italy and ^cStudy Coordinating Centre, Laboratory of Hypertension, Department of Molecular and Cardiovascular Research, University of Leuven, Leuven, Belgium.

Correspondence and requests for reprints to Gianfranco Parati, II Cardiology Unit, University of Milano-Bicocca and S. Luca Hospital, Via Spagnoleto, 3, 20149 Milan, Italy.
Tel: +39 02 582161; fax: +39 02 58216956; e-mail: gianfranco.parati@unimib.it

See original paper on page 1291

In this issue of the journal, Smith *et al.* [1] illustrate the results of a meta-analysis of studies aimed at comparing the blood pressure effects of different antihypertensive drugs through use of ambulatory blood pressure monitoring (ABPM). These studies were subdivided into two groups, according to whether they were based on a conventional double-blind, placebo-controlled (DBPC) approach or on the more recently proposed prospective, randomized, open-label, blinded-endpoint (PROBE) method [2]. The aim of the paper by Smith *et al.* [1] was to assess whether the results of trials on antihypertensive treatment are comparable, in terms of drug-induced blood pressure reduction, when using a PROBE rather than the more conventional DBPC design. The five studies selected (two with the DBPC design and three with the PROBE design) had a parallel-group structure and were identified in the context of a clinical programme aimed at evaluating the features of a specific angiotensin II receptor blocker. The authors conclude that changes in mean 24-h ambulatory blood pressure values derived from the DBPC and PROBE trials included in their meta-analysis are statistically equivalent when the aim is to rule out a difference of ≥ 3 mmHg in systolic and/or ≥ 2 mmHg in diastolic blood pressure on comparing the two drugs. They also conclude that these data support the validity of a PROBE design in assessing antihypertensive efficacy based on blind ABPM measurements.

Advantages of ABPM in the design of antihypertensive drug trials

Blood pressure is characterized by high variability, and a single reading taken at a given time, or even multiple readings obtained on different days, will only partially

reflect a subject's mean blood pressure over a whole day [3,4]. Furthermore, the clinical environment and the presence of the observer may arouse the subject, which can lead to an overestimation of blood pressure if a conventional approach is used [5–7]. ABPM addresses several of the shortfalls of conventional blood pressure measurement [8,9] and can be used in clinical trials to select patients with sustained rather than isolated office hypertension (also defined as 'white-coat hypertension') [10], to increase the precision in estimating the effects of blood pressure-lowering drugs, or to decrease sample size in cross-over trials [11].

Smith *et al.* [1] emphasize this point, and further suggest that ABPM limits the need for a control arm in clinical trials, because mean 24-h ambulatory blood pressure is minimally affected by placebo.

Whether the blood pressure detected by ambulatory monitoring is actually influenced by a placebo effect remains a matter for debate. The issue is important because it impacts on the design of clinical trials in hypertension. Some experts [12] argue that ambulatory monitoring eliminates only observer bias and expectation and does not remove regression to the mean and patient-related factors that contribute to the placebo effect. Other researchers hypothesize that ambulatory monitoring would make control observations with placebo redundant [13,14]. If this were true, investigators making use of ABPM could investigate antihypertensive interventions simply by comparing the blood pressures before and after administration of a given treatment. The intra-arterially monitored blood pressure has been shown to remain at a constant level when

hypertensive patients were administered placebo for 6 weeks [15]. Similarly, in a 6-week study with a non-invasive recording technique [16], ambulatory blood pressure fell only slightly during the initial hours of the recording, and the mean blood pressure over 24-h remained unaffected. On balance, most publications favour the view that, over a period of a few weeks, the ambulatory blood pressure does not decrease with placebo. However, long-term studies gave different results [17]. Analysis of the database of the Systolic Hypertension in Europe trial (Syst-Eur) [18] demonstrated that, in long-term trials, not accounting for placebo effects could lead to an overestimation of the true effects of antihypertensive drugs when using ABPM. After 1 year of follow-up, the blood pressure decrease in the placebo arm of the Syst-Eur trial ($n = 169$) amounted to 20–40% of the corresponding change observed under active treatment ($n = 168$). This was true both for the conventional and for the ambulatory measurements [18]. However, these observations have to be interpreted cautiously because long-term changes in blood pressure may be influenced not only by a placebo effect, but also by other factors such as changes in lifestyle or intercurrent illnesses.

Whether or not there is a significant placebo effect when the blood pressure is measured by ambulatory monitoring is largely an academic discussion in the context of the multiple and different evaluations that are performed in a drug trial. Indeed, to evaluate drug effects other than the blood pressure reduction *per se*, such as side-effects or effects on organ damage and events rate, a control group is always necessary. The best trial design, in this regard, requires masking both the patient and the observer. PROBE trials might be cheaper and simpler than DBPC ones, but are less precise in this context (see below).

Smith and colleagues also suggest that because of the greater variability of office blood pressure values compared to ABPM, a larger sample of patients might be required to have the same power with regard to statistical inferences concerning blood pressure effects, when comparing drug-induced changes of office blood pressure in DBPC and PROBE design studies. This is certainly the case in cross-over trials [12,13]. However, by contrast to what is often perceived, the advantage of the higher reproducibility of ambulatory blood pressure is lost in trials with a parallel-group design [11], such as those selected for this meta-analysis. Reducing the sample size is also not possible when the aim of a study is to investigate the effects of an antihypertensive agent on the diurnal profile of blood pressure [11].

However, in spite of these problems, Smith *et al.* [1] are correct when they emphasize that a PROBE design could be considered only when focusing on 'objective'

blood pressure determination. As they point out in their paper, comparing the drug-induced blood pressure changes in DBPC and PROBE design studies by means of office blood pressure measurements would hardly be acceptable because focusing on office blood pressure readings would mean lacking any blinded endpoint, this would imply that physician's and patient's biases cannot be eliminated. Finally, use of office blood pressure readings would not allow the comparison between the information provided by these two approaches on the degree of blood pressure control over 24 h, the daytime and the night-time. In particular, focus on office blood pressure readings only would prevent any comparison of the ability of these different methods to assess drug-induced changes in hourly blood pressure profiles, in blood pressure overall variability or in the degree of morning blood pressure surge [19]. This would also be the case when the time distribution of the antihypertensive effect is investigated by assessing the duration of action of a given compound, and the homogeneity of its blood pressure lowering action over 24 h, through the use of mathematical indices such as the trough-to-peak ratio or the smoothness index [20–22].

Double-blind, placebo-controlled versus prospective, open-label, blinded-endpoint study design

Properly designed, randomized, double-blind, placebo-controlled (DBPC) trials are presently regarded as the 'gold standard' in the field of clinical studies aimed at evaluating antihypertensive drug efficacy. This is reflected by the fact that regulatory authorities in several countries, as well as at the international level, require evidence of efficacy or safety from DBPC trials for antihypertensive drug registration or approval purposes [23]. However, as pointed out by Smith *et al.* [1], DBPC trials have some disadvantages [1]. They have a high cost and are time-consuming both for the hospital staff involved, as well as for the recruited patients. Moreover, physicians and/or their patients may be reluctant to accept the possibility of a prolonged period of blind treatment, particularly if the control is placebo or if the recruited patients are characterized by an increased cardiovascular risk profile. PROBE design studies do not share these difficulties and may thus appear as a simpler, cheaper and more attractive alternative in several instances, in particular when applied to studies taking advantage of all the positive features of ABPM. PROBE design studies may offer the possibility of an unbiased data collection only when changes in objectively determined endpoints (e.g. automated blood pressure measurements) are considered however. This is certainly not the case when collecting information on treatment side-effects, as well as when assessing the impact of treatment on organ damage or events rate. Indeed, the blinded validation of disease outcomes in open trials

does not rule out the possibility that prior knowledge of treatment allocation results in selective over- or under-reporting of events, as well as in biased detection of organ damage changes. This might explain why rates of common side-effects to major drug classes are usually twice as high in open compared to double-blind trials.

Moreover, a PROBE design may be affected by selection bias when recruiting patients. Although, theoretically, this should not occur because a randomization process is implemented aimed at preventing this inconvenience, the open design features of PROBE might expose local investigators to the influence of the clinical information they have access to, thus interfering with a truly blinded randomization of patients.

Finally, some caution in concluding on the correspondence between DBPC and PROBE design trials is also suggested by the peculiar selection of studies included in the meta-analysis by Smith *et al.* [1], who focus on data obtained from a clinical database built when comparing the properties of a specific angiotensin II receptor blocker with those of other drugs. This was carried out by considering studies that are not always strictly comparable in the subjects' selection criteria, duration of data collection and previous antihypertensive drug regimens. Moreover, the question of whether the authors' results would be confirmed when considering studies carried out according to different methodological approaches (e.g. by using automated self-blood pressure monitoring at home) remains unaddressed.

In conclusion, the study by Smith *et al.* [1] appears to offer an interesting contribution to the discussion on the methodology of drug trials, and provides evidence that DBPC and PROBE design studies offer similar information on ambulatory blood pressure reduction in trials aimed at comparing different antihypertensive drugs. However, their results should not lead to the more generalized conclusion that DBPC and PROBE design studies are to be considered as largely equivalent when organizing antihypertensive drug trials. By contrast, there are several instances when a double-blind, placebo-controlled approach still appears to be necessary. This is the case when collecting data on the effects of drugs on parameters other than the objective information represented by automated, computerized ambulatory blood pressure measurements, such as changes in clinic blood pressure, side-effects and other clinical endpoints. Furthermore, this is also the case when a true blinded randomization of recruited subjects has to be enforced.

Therefore, caution and great methodological care are needed when the decision to adopt a PROBE design is taken, even when the trial initially appears to be focused only on blindly and objectively determined endpoints.

References

- 1 Smith DHG, Neutel JM, Lacourcière Y, Kempthorne-Rawson J. Prospective, randomized, open-label, blinded-endpoint (PROBE) designed trials yield the same results as double blind, placebo-controlled trials with respect to ABPM measurements. *J Hypertens* 2003; **21**:1291–1298.
- 2 Hansson L, Hedner T, Dahlöf BP. Prospective randomized open blinded end-point (PROBE) study. A novel design for intervention trials. *Blood Press* 1992; **1**:113–119.
- 3 Mancia G, Ferrari A, Gregorini L, Parati G, Pomidossi G, Grassi G, Zanchetti A. BP and heart rate variabilities in normotensive and hypertensive human beings. *Circ Res* 1983; **53**:96–104.
- 4 Mancia G, Parati G, Di Rienzo M, Zanchetti A. Blood pressure variability. In: Zanchetti A, Mancia G (editors): *Handbook of hypertension, vol. 17: pathophysiology of hypertension*. Amsterdam: Elsevier Science BV; 1997, pp. 117–169.
- 5 Mancia G, Bertinieri G, Grassi G, Parati G, Pomidossi G, Ferrari A, *et al.* Effects of blood pressure measurements by the doctor on the patient's blood pressure and heart rate. *Lancet* 1983; **2**:695–698.
- 6 Mancia G, Parati G, Pomidossi G, Grassi G, Casadei R, Zanchetti A. Alerting reaction and rise in blood pressure during measurements by physician and nurse. *Hypertension* 1987; **9**:209–215.
- 7 Khattar RS, Senior R, Lahiri A. Cardiovascular outcome in white-coat versus sustained mild hypertension. A 10 year follow-up study. *Circulation* 1998; **98**:1892–1897.
- 8 Parati G, Pomidossi G, Casadei R, Mancia G. Lack of alerting reactions and pressor responses to intermittent cuff inflation during non invasive blood pressure monitoring. *Hypertension* 1985; **7**:597–601.
- 9 Mancia G, Di Rienzo M, Parati G. Ambulatory blood pressure monitoring. Research and clinical applications. *Hypertension* 1993; **21**:510–524.
- 10 Sareli P, Radevski IV, Valtchanova ZP, Libhaber E, Candy GP, Den Hond E, *et al.* Efficacy of different drug classes used to initiate antihypertensive treatment in Black subjects. *Arch Intern Med* 2001; **161**:965–971.
- 11 Staessen JA, Thijs L, Parati G, Mancia G, O'Brien ET, on behalf of the Syst-Eur Investigators. Clinical trials with ambulatory blood pressure monitoring: fewer patients needed? *Lancet* 1994; **344**:1552–1556.
- 12 Mansoor GA, White WB. Contribution of ambulatory blood pressure monitoring to the design and analysis of antihypertensive therapy trials. *J Cardiovasc Risk* 1994; **1**:136–142.
- 13 Conway J, Johnson J, Coats A, Somers V, Sleight P. The use of ABPM to improve the accuracy and reduce numbers of subjects in clinical trials of antihypertensive treatment. *J Hypertens* 1988; **6**:111–116.
- 14 Mancia G, Omboni S, Parati G, Ravogli A, Villani A, Zanchetti A. Lack of placebo effect on ambulatory blood pressure. *Am J Hypertens* 1995; **8**:311–315.
- 15 Gould BA, Mann S, Davies AB, Altman DG, Raftery EB. Does placebo lower blood pressure? *Lancet* 1981; **2**: 1377–1381.
- 16 Multi E, Trazzi S, Omboni S, Parati G, Mancia G. Effect of placebo on 24-h non-invasive ambulatory blood pressure. *J Hypertens* 1994; **12**:1035–1039.
- 17 Staessen JA, Thijs L, Clement D, Davidson C, Fagard R, Lehtonen A, *et al.*, on behalf of the Syst-Eur Investigators. The ambulatory blood pressure decreases on long-term placebo treatment in older patients with isolated systolic hypertension. *J Hypertens* 1994; **12**:1035–1039.
- 18 Staessen JA, Thijs L, Bieniaszewski L, O'Brien ET, Palatini P, Davidson C, *et al.* On behalf of the Syst-Eur Investigators. Ambulatory monitoring uncorrected for placebo overestimates long-term antihypertensive action. *Hypertension* 1996; **27**:414–420.
- 19 Mancia G, Omboni S, Ravogli A, Parati G, Zanchetti A. ABPM in the evaluation of antihypertensive treatment: additional information from a large data base. *Blood Press* 1995; **4**:148–156.
- 20 Lipicky RJ. Trough: peak ratio: the rationale behind the United States Food and Drug Administration recommendations. *J Hypertens* 1994; **12** (suppl 8):S17–S19.
- 21 Omboni S, Fogari R, Palatini P, Rappelli A, Mancia G. Reproducibility and clinical value of the trough-to-peak ratio of the anti-hypertensive effect: evidence from the SAMPLE study. *Hypertension* 1998; **32**:424–429.
- 22 Parati G, Omboni S, Rizzoni D, Agabiti-Rosei E, Mancia G. The smoothness index: a new, reproducible and clinically relevant measure of the homogeneity of the blood pressure reduction with treatment for hypertension. *J Hypertens* 1998; **16**:1685–1691.
- 23 ICH Steering Committee. Principles for clinical evaluation of new antihypertensive drugs: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. *Int Dig Health Legis* 1997; **48**:231–234.